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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/044,569	01/11/2002	Jean-Marie R. Saint-Remy	920522-905380	9454

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,569	SAINT-REMY ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,13-20 and 22-31* is/are pending in the application.

4a) Of the above claim(s) *2-4 and 13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 10/25, is acknowledged.

2. Claims 2-4,13-20 and 22-31 are pending.

3. Claims 2-4,13-20 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 22-31 are under consideration in the instant application as they read on as they read on a method for preventing and/or treating the systemic inflammatory response syndrome with a partial inhibitor of factor VIII, wherein the partial inhibitor is an antibody and the antibody that is produce by KRIX 1 or anti-fVIII C1 domain antibody.

5. Claims 27-28 are objected to because of the following informalities: the word "where" recited in claim 27, line 1, should be changed to "wherein". Further, the alternative operator "or" recited in claim 28, which should be only before the last term of a series, has been recited twice, once after Fab` and the second time after $F(ab`)_2$. Correction is required.

6. In view of the amendment filed on 10/25/04, the following rejections are necessitated by the amendment.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 31 is indefinite and ambiguous in the recitation of "the amino acid sequence depicted in figure 8/9". Figures 8 and 9 depict no sequences but rather fig. 8 shows plasma concentrations of α2-antiplasmin in wild-type C57B1/6 mice and in factor VIII knock-out mice after injection of lipopolysaccharide. FIG. 9 shows plasma concentrations of fibrinogen in wild-type C57B1/6 mice and in factor VIII knock-out mice after injection of lipopolysaccharide. It is unclear what amino acid sequences are claimed.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "80% identical to the amino acid sequence depicted in figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9" claimed in claim 31, line 2-4 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 9/25/04 points to the specification on paragraph 31 and 48 for support for the newly added limitation "80% identical to the amino acid sequence depicted in figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9" as claimed in claim 31. The Examiner notes that paragraph 31 of the specification refers to ligands rather than antibodies. Paragraph 48 of the specification does not provide a clear support for such limitations, the at least 80% homology is referred to the intact antibody or the CDRs, rather than V_H or V_L sequences. The instant claim now recites a limitation which was not clearly disclosed in the specification and recited in the claims as originally filed.

11. In view of the amendment filed on 10/25/04, only the following rejections are remained.

12. Claim 22-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action mailed 4/21/04.

Applicant's arguments, filed 10/25/04, have been fully considered, but have not been found convincing.

Applicant argues that the deposit is present in a public depository and in accordance with rule 9.1 or the Budapest Treaty. Further, Applicant presents a copy of the receipt provided to Applicant by the BCCM indicating the deposit was received under the Budapest Treaty, as well as the requested statement with regard to its availability. Applicant contends that given the statement and Applicant's declaration Applicant maintains that the requirements of section 112.

While the Examiner acknowledges the copy receipt provided by BCCM indicating the deposit of KRIX-1 cell line, however, Applicant's statement, filed 10/25/04, does not satisfies the requirement for the deposit of the biological material KRIX-1 (LMBP 5089) under 35 USC § 112, first paragraph because applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Further, the specification does not reasonably provide **enablement** a method for preventing and/or treating Systemic Inflammatory Response Syndrome in a mammal by administering a partial inhibitor of factor VIII to the said mammal which is a monoclonal antibody against Factor VIII or an antigen binding fragment of said monoclonal antibody, said antibody or fragment being able to recognize epitopes located in the C1 domain of Factor VIII in claim 22, wherein the monoclonal antibody is produced by on purpose immunization in animals in claim 23, or mouse in claim 24, wherein said monoclonal antibody is of class IgG in claim 25, wherein said monoclonal antibody is a humanized monoclonal antibody in claim 26, wherein said monoclonal antibody is the antibody obtainable from the cell line named KRIX 1 deposited with the Belgian Coordinated Collections of Microoganisms under accession number LMBP 5089CB in claim 27, wherein said antigen-bindign fragment is an Fab, Gab', fab(ab')2 or scFV in claim 28, wherein said monoclonal antibody or fragment is administered in an anti-thrombin and/or activated protein C and or tissue factor pathway inhibitor plasma level restoring amount in claim 29, the method further comprising the sequenctial administration of a therapeutically effective amount of heparin in claim 30, wherein said monoclonal antibody or fragment of said antibody comprises a variable heavy sequence being at lest 80% identical to the amion acid sequence depicted I figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9 in claim 31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 4/21/04.

Further, in view of applicant comment regarding the sepsis as a particular embodiment of the claims, the following rejection applies to the claimed sepsis. Freeman et al teaches that mediator-specific antagonists, high dose glucocorticoids, and endotoxin-directed therapies, were administered initially in animal models with promising results. Their administration to human, however, proved disappointing, prompting questions regarding both the initial hypothesis and the value of animal studies in modeling human sepsis. Freeman et al further teach that many issues pertaining to the pathophysiology and treatment of sepsis remain unresolved (see page 973-974, under conclusion). Due to the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed method with a reasonable expectation of success.

Regarding the 80% homology language in claim 31, it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding

function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the antibody as defined by the claims which may contain less than the full complement of CDRs (due to up to 20% modifications of VH and/or VL) from the heavy and light chain variable regions of an fVIII antibody have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the antibodies of invention commensurate with the scope of the claims from the written disclosure alone.

Applicant's arguments, filed 10/25/04, have been fully considered, but have not been found convincing.

Regarding the *in vitro* studies do not correlate well with *in vivo* clinical trial results in patients, Applicant submits a declaration form one of the inventors, Dr. Jean-Marie Saint-Remy, which provide additional *in vivo* data of an anti-FVIII C1 domain antibody, which is a partial inhibitor of FVIII in mice, and demonstrate that it can be administered in elevated dosages without the side effects typically observed fro complete FVIII inhibitors and that it is capable of preventing LPS-induced shock in a well established mouse model.

However, the declaration filed under 37 CFR1.132 by Dr. Jean-Marie Saint-Remy filed on 10/25/04 is insufficient to over come the rejection under 35 USC 112, enablement rejection, because the declaration is not considered sine it is presented in an unexecutable form (i.e. unsigned and undated declaration).

Regarding Taylor et al (1997) reference, Applicant submits that Taylor et al teach that the syndrome has elements that are similar to those observed in diffused intravascular coagulation, thrombotic thrombocytopenic purpura, and hemolytic uremic synsufficient drome. Further Applicant points to the statement in Taylor's et al reference that platelets at least in part mediate the tissue damage associated with these syndromes. Based on this, Applicant concluded that Taylor himself indicates that the C4bBP and *E. coli* treatment only partially-mimics the mentioned disorders and based thereon concludes that at a treatment at the level of platelet aggregation will not be only partial solution fro curing these disorders.

However, if the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied. "The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements...However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually

does not provide an adequate basis to support generic claims." MPEP § 2164.03. "Substantiating evidence may be in the form of animal tests which constitute recognized screening procedures with clear relevance to utility in humans. See Ex parte Krepelka, 231 USPQ 746 (Board of Patent Appeals and Interferences 1986) and cases cited therein." Ex parte Maas, 9 USPQ2d 1746. In the instant case Taylor et al explicitly teach that the differences in pathophysiology between the animal model and each of the human disorders makes it very difficult to extrapolate from this model to human disease (see pg 4083 last paragraph in particular).

Applicant contends that the notion of the fact that a non-perfect model was used for the disorders studied, is also mentioned at the end of the discussion of the article. Applicant contends that from this it can be deduced that Taylor ascribes the differences in pathophysiology between the animal model and each of the human disorders not to the differences between baboon and man but rather to the differences between the model and the disorders themselves. Applicant submits that the Taylor article at most suggests that it is difficult to extrapolate from a model which in his opinion only reflects some aspects of the actual disease as observed in humans, and that the article gives no warnings of extrapolating baboon results to humans.

However it is noted that the specification does not provide exemplification or alternative animal model to prevent and/or treat human patients with SIRS/sepsis neither does the specification provide clear solutions to the pathophysiological condition from the baboon model. Applicant's disclosure does not appear to have provided the skilled artisan with sufficient guidance and support as how to reach the development of effective *in vivo* human therapeutic methods, commensurate in scope with the claimed invention.

13. Claim 22-31 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of *in vitro* method of partially inhibit thrombin formation with anti-fVIII C1 domain antibody.

Applicant is not in possession of a method for preventing and/or treating Systemic Inflammatory Response Syndrome in a mammal by administering a partial inhibitor of factor VIII to the said mammal which is a monoclonal antibody against Factor VIII or an antigen binding fragment of said monoclonal antibody, said antibody or fragment being able to recognize epitopes located in the C1 domain of Factor VIII in claim 22, wherein monoclonal antibody or fragment of said antibody comprises a variable heavy sequence being at lest 80% identical to the amion acid sequence depicted I figure 8 and/or a variable light chain sequence being at least 80% identical to the amino acid sequence depicted in figure 9 in claim 31.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification

provides neither a representative number of species (of antibody comprises a variable heavy sequence being at least 80% identical VH and/or VL) to describe the claimed genus, nor does it provide a description of structural features that are common to species. As discussed above, the specification provides no structural description of such antibodies other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed the monoclonal antibody sequences looks like.

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
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November 30, 2004

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